REMARKS

Applicant wishes to express its appreciation for the Examiner's time and courtesies in connection with the telephone interview conducted on November 21, 2008.

As discussed during the interview, Applicant has amended Claim 23 in several respects, namely: to correct the typographical error of "reprcoterol," which is now correctly recited as "reproterol"; to recite "wherein said bronchodilator is substantially completely insoluble in said fluorocarbon propellant" support for which may be found in page 3 (last line), for example; to remove the recitations "further," "about" and "wherein said canister fits into the actuator"; to enumerate the recited elements of the aerosol composition as "(i)-(iii)"; and to delete the phrase "or a salt thereof" and replace it with the recitation "or a salt of said bronchodilator." Applicant has canceled claim 28. Claims 31-47 are new, support for which may be found throughout the specification, *e.g.*, the example in p. 5. With regards to new claims 40 and 42-44, the percent amounts of concentration in mixture by weight (w/w) were calculated using the weights of the ingredients in the example in p. 5 and rounding to the nearest tenth for consistency. For example the recitation in claim 40 of "0.4%" salbutamol sulfate was derived by dividing the weight of salbutamol sulfate (0.03g) by the total weight of the ingredients, *i.e.*, 0.03g/(0.03g + 0.97g + 7.5g) to arrive at 0.35%, which was rounded to 0.4%. Accordingly, no new matter has been added by these amendments. Applicant respectfully requests entry of these amendments.

Claim Objections

Claim 23 has been objected to because of a typographical error. Applicant has corrected the recitation of "reprcoterol" in Claim 23, line 10 to read "reproterol."

Claim Rejections - 35 USC § 112

Claims 23-30 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner has determined that the present specification does not provide support for the recitation "an actuator with a spray orifice aperture of from about 100 to about 300 microns, wherein said canister fits into the actuator."

The third full paragraph in page 5 of the present specification (publication WO 98/05302), teaches an actuator with a spray orifice aperture "between 100-300 microns." Applicant has removed the recitation "wherein said canister fits into the actuator." Thus, the claim as amended, which recites *inter alia* "an actuator with a spray orifice aperture of from 100 to 300 microns," is clearly supported by the specification. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection.

Claims 23-30 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner has alleged that the recitation "bronchodilator selected from the group consisting of...tolubuterol and orciprenaline or a salt thereof, a fluorocarbon propellant, and 6% to 25% of a polar co-solvent" is not clear. Specifically, the Examiner has alleged that it is unclear if all disclosed components are part of the Markush group and whether the recitation "or salt thereof" refers just to orciprenaline or all bronchodilators of the Markush group.

The rejection is moot with respect to cancelled claim 28. Applicant has amended Claim 23 by organizing the recitations under (i)-(iii), and to recite "or a salt of said bronchodilator," to clarify that salts of the recited

bronchodilators are embraced by the claims. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection.

Claim Rejections - 35 USC § 103

Claims 23-26 and 28-30 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over *Schultz* WO 93/11747 ("*Schultz* 747"), in view of *Schultz, et al.*, U.S. Patent 5,899,201 ("*Schultz* 201"). The Office has determined that it would have been obvious to combine the teachings of *Schultz* '747 with the teachings of *Schultz* '201 to yield the claimed invention. Specifically, the Office holds the view that *Schultz* '747 teaches all limitations in Claim 23 except the actuator, which is taught in *Schultz* '201 as having an exit orifice from about 0.25 mm (250 microns). Thus, the determination is that it would have been obvious to one of ordinary skill in the art to modify the aerosol canister of *Schultz* '747 to include the actuator in *Schultz* '201, because *Schultz* '201 teaches that when compared to a conventional actuator, the actuator of *Schultz* '201 is capable of delivering a dose of drug in the form of an aerosol such that more drug reaches the area of the lung where it is therapeutically effective, and less drug is deposited in the mouth and throat, thus decreasing the undesired systemic effects of the drug. Applicant respectfully traverses this rejection as it applies to claims 23-26, 29 and 30, and as it would have prospectively been applied to claims 31-47.

Schultz '747 teaches suspension aerosol formulations in which ethanol is explicitly taught as "optional" (p. 9, ll. 26). More significantly, however, there is no detail regarding the valve assembly. *Schultz* '747 merely states that "appropriate valve assemblies for use with aerosol formulations is dependent upon the particular surfactants or adjuvant used (if any), on the propellant, and on the

particular drug being used." (p. 11, ll. 16-20). There are no more specific teachings as to exactly how the valve assemblies depend on these factors, however.

The teachings of *Schultz* '201 do not fill the void of *Schultz* '747, especially in terms of the size of the orifice, so as to provide any rationale by which a person skilled in the art would have arrived at the claimed invention. *Schultz* '201 teaches improved delivery of solution or suspension medicinal aerosol formulations by the addition of a constriction aperture to a conventional actuator. In describing exit orifices of conventional actuators, Col. 4, ll. 1-2 of *Schultz* '201 discloses that common minimum exit orifice diameters range from about 0.25 mm (250 microns) to about 0.64 mm (640 microns). In that same paragraph, *Schultz* '201 also teaches that "[w]ith conventional actuators *wider diameters* commonly are used in connection with *suspension aerosol* formulations." (Col. 4, ll. 1-4, emphasis added)[1]. *Schultz* goes on to explain that "[n]arrower diameters are used in connection with solution aerosol formulations and with suspension aerosol formulations that are particularly difficult to deliver in the form of an aerosol containing a high respirable mass." (Col. 4, ll. 5-8).

Thus, when the paragraph bridging Cols. 3-4 in *Schultz* '201 is considered in its entirety, it becomes clear that a person skilled in the art would have selected an orifice diameter greater than 300 microns and well at the higher end of the 0.25 mm - 0.64 mm (250 - 640 microns) range for a suspension aerosol formulation. This view is entirely consistent with working examples in *Schultz* '201 that describe

[1] It is impermissible within the framework of 35 U.S.C. § 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art. *See, In re Mercer*, 515 F.2d 1161, 1165-66, 185 U.S.P.Q. 774, 778 (C.C.P.A. 1975); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 230 U.S.P.Q. 416 (Fed. Cir. 1986).

a standard suspension actuator having an exit orifice diameter of 0.56 mm (560 microns). *See Schultz* '201 Col. 6, ll. 1-4. Thus, the diameters of the orifices taught in *Schultz* '201 for delivering a suspension aerosol formulation are outside, and much greater (*e.g.*, about 2 to 5 times greater) than the range of 100 to 300 microns as recited in the independent claims. As such, *Schultz* '201 in fact teaches away from the claimed invention. To further highlight this distinction, Claim 23 recites that the bronchodilator is "substantially completely insoluble" in the propellant. In addition to this recitation, the three new independent claims 39, 46 and 47 also recite that the aerosol formulation is a "suspension" aerosol formulation (support for which is found in bottom of page 5, for example). Thus, the present claims now clearly point out that the aerosol formulation is in the form of a suspension as opposed to a solution.

Subsequent disclosures in *Schultz* '201, and particularly the comparative experimentation (the results of which are set forth in tables 2 and 3) are also believed to be probative of non-obviousness. Table 2 shows the results of an experiment in which 4 actuators (standard suspension - exit orifice of 0.56 mm; standard solution - exit orifice 0.254 mm; actuator 1 - exit orifice of 0.56 mm with constriction aperture; actuator 8 - exit orifice of 0.254 mm with constriction aperture) were tested with a solution aerosol formulation. As explained in col. 6, lines 28-34, the results showed that actuator 1 delivered a higher respirable fraction and lower percentage of medicament retained on the throat (more desirable) as compared with the other actuators. Thus, when wider exit orifices (0.56 mm) were used in conjunction with *Schultz's* invention *i.e.*, a constriction aperture, solution aerosol formulation delivery was improved.

Table 3 shows the results of another experiment which compared three actuators (actuator 1 - exit orifice of

0.56 mm and constriction aperture; a standard suspension actuator - exit orifice of 0.56 mm; a standard solution actuator - exit orifice of 0.254 mm) with a formulation containing pirbuterol acetate and a propellant (Formulation A) or a formulation containing pirbuterol acetate, ethanol, oleic acid and propellant (formulation B). Actuator 1 provided higher respirable mass with less drug retention on the throat than a conventional actuator when tested with the formulations. Thus, use of a standard suspension exit orifice (0.56 mm), in combination with *Schultz's* invention which includes the constriction aperture, was found to improve delivery of suspension formulations. The data in table 3 also show that when a pirbuterol formulation was delivered through a standard solution actuator (*i.e.*, exit orifice of 0.254 mm with formulation A), much less respirable mass of the drug was delivered and a much greater amount was retained on the throat, as compared to delivery of the same formulation via the suspension aerosol actuator.

In summary, the teachings in *Schultz* '201 from Col. 4, ll. 12-14 with respect to exit orifices may be summarized thusly: 1) suspension aerosol formulations most often require relatively wide exit orifices *e.g.*, 0.56 mm or 560 microns; and 2) these wider exit orifices can be used in combination with *Schultz's* invention regardless of the type of aerosol formulation (solution or suspension). Either way, the person of ordinary skill would have been led in a direction opposite to that of the claimed invention. Indeed, in col. 4, lines 12-14, Schultz '201 expressly states that his inventive actuator "obviates the need for the use of narrow exit orifices." The fact that Applicant proceeded in a manner contrary to the teachings of *Schultz* '201 by using a far narrower orifice for a suspension formulation as compared to the standard suspension orifices described in *Schultz* '201 is strongly indicative of nonobviousness. *See Kloster Speedsteel*

AB v. Crucible Inc., 793 F.2d 1565, 230 U.S.P.Q. 81, 86 (Fed.Cir.1986)(holding that the inventor achieving the claimed invention by doing what those skilled in the art suggested should not be done is in fact strongly probative of nonobviousness).

Due to the Applicant's innovation by looking beyond what the prior art teaches, it has been discovered that increasing the concentration of polar co-solvent in a suspension aerosol formulation enables the use of much narrower orifices. Persons of ordinary skill in the art are not innovators; rather they will typically look to the art commonly known in the field as a guide to solve a particular problem. With that in mind, patentability is to be assessed from the perspective of the hypothetical person of ordinary skill in the art; not from the perspective of the inventors, who are presumed to be persons of extraordinary skill. *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454, 227 U.S.P.Q. 293, 297 (Fed. Cir. 1985) (which notes that the person of ordinary skill is an objective legal construct presumed to think along conventional lines without undertaking to innovate, whether by systematic research or by extraordinary insights).

Given this standard, persons of ordinary skill would not have ignored the clear teachings of *Schultz* '201 regarding the size of the apertures especially since the formulations taught in *Schultz* '747 are also explicitly described as suspension aerosols. Moreover, there is no suggestion whatsoever in *Schultz* '747 or *Schultz* '201 that the presence of a polar co-solvent at concentrations of 6-25% would alleviate the need for wider apertures and actually allow for narrower apertures to be used with a suspension aerosol formulation as recited in the present claims.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of this rejection.

Claim 27 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over *Schultz* WO 93/11747, in view of *Schultz, et al.*, U.S. Patent 5,899,201 and *Greenleaf, et al.* U.S. Patent 5,348,730. The Examiner has alleged that *Greenleaf* teaches bronchodilators such as epinephrine, phenylepinephrine, and salbutamol. Thus, it has been determined that it would have been obvious to one of ordinary skill in the art to include salbutamol in the suspension formulation of *Schultz*, because *Greenleaf* teaches salbutamol is a known bronchodilator among other bronchodilators, and because *Schultz* teaches a suspension aerosol formulation suitable for a wide variety of bronchodilators. Applicant respectfully traverses this rejection.

Greenleaf does not provide any teaching or rationale to overcome the shortcomings of the collective teachings of *Schultz* '747 and *Schultz* '201. *Greenleaf* does not teach an actuator with a spray orifice having an aperture of from 100 to 300 microns. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection.

Applicant submits that claims 23-27 and 29-47 are patentable over the cited prior art and are thus in condition for allowance.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

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Respectfully submitted,

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